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Abuse and diversion of buprenorphine sublingual tablets and film



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ABSTRACT

Buprenorphine abuse is common worldwide. Rates of abuse and diversion of three sublingual buprenorphine formulations (single ingredient tablets; naloxone combination tablets and film) were compared. Data were obtained from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS[®]) System Poison Center, Drug Diversion, Opioid Treatment (OTP), Survey of Key Informants' Patients (SKIP), and College Survey Programs through December 2012. To control for drug availability, event ratios (rates) were calculated quarterly, based on the number of patients filling prescriptions for each formulation ("unique recipients of a dispensed drug," URDD) and averaged and compared using negative binomial regression. Abuse rates in the OTP, SKIP, and College Survey Programs were greatest for single ingredient tablets, and abuse rates in the Poison Center Program and illicit diversion rates were greatest for the combination tablets. Combination film rates were significantly less than rates for either tablet formulation in all programs. No geographic pattern could be discerned.

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1. Introduction

Buprenorphine sublingual formulations are approved in the United States (US) for the treatment of opioid dependence (FDA, 2002). Buprenorphine therapy improves retention in substance abuse treatment, decreases emergency department utilization and high-risk sexual behaviors, and improves overall quality of life (Maremmanni, Pani, Pacini, & Perugi, 2007; Schwarz, Zelenev, Bruce, & Altice, 2012; Sullivan et al., 2008). Buprenorphine is a long-acting partial agonist of the μ -opioid receptor, a full κ -receptor antagonist, and an ORL-1

partial agonist (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). Buprenorphine exhibits a ceiling agonist effect at high doses, and because of its high affinity for the μ -receptor buprenorphine can interfere with the binding of pure μ -agonists, such as morphine. Because of this, concurrent use of buprenorphine blocks the "high" ordinarily received from abuse of high-potency opioid agonists, such as hydromorphone, and early studies suggested that abuse liability was low by the sublingual route (Walsh & Eissenberg, 2003).

Sublingual buprenorphine is available in the US in three formulations. The single ingredient and naloxone combination tablet formulations were introduced in the US in January 2003, and a mucoadhesive combination film formulation was introduced in September 2010. In the combination tablets and film, naloxone is incorporated in a fixed ratio (1 mg naloxone per 4 mg buprenorphine) to deter abuse by parenteral routes, such as nasal insufflation ("snorting") or injection (Fudala & Johnson, 2006; Mendelson & Jones, 2003). Although use for off-label indications has been described, the most common and only approved use of buprenorphine sublingual formulations in the US is for office-based treatment of opioid dependence, an indication for which its overall safety and effectiveness has been established (Amass et al., 2004; Fiellin & O'Connor, 2002; Johnson, Jaffe, & Fudala, 1992; Mattick, Kimber, Breen, & Davoli, 2008). In the final quarter of 2012, approximately 750,000 patients

Abbreviations: CI, 95% Confidence interval; FDA, United States Food and Drug Administration; IRB, Institutional review board; OTP, Opioid Treatment Program; REMS, Risk evaluation and mitigation strategy; SKIP, Survey of Key Informants' Patients; URDD, Unique recipients of a dispensed drug; US, United States.

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filled prescriptions for buprenorphine in the US (IMS Health Solutions, unpublished data). Generic formulations of single ingredient buprenorphine tablets have been available in the US since late 2009, and combination tablets since February 2013.

Data from several US sources demonstrate that buprenorphine sublingual formulations are diverted and utilized outside of an established physician–patient relationship, both for self-medication of withdrawal symptoms and to produce euphoria (Daniulaityte, Falck, & Carlson, 2012; Yokell, Zaller, Green, & Rich, 2011). To date, few studies have directly compared abuse and diversion rates of buprenorphine single ingredient and combination tablet formulations, and abuse and diversion rates for the combination film have not been reported (Comer & Collins, 2002; Dasgupta et al., 2010; Johanson, Arfken, di Menza, & Schuster, 2012).

The purpose of this study was to measure and compare rates of diversion and abuse of the three formulations of sublingual buprenorphine available in the US.

2. Materials and methods

2.1. Data source

Data were obtained from five programs of the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System, as described below. Methods of the RADARS System and its component programs have been described previously (Inciardi et al., 2009). In all RADARS System Programs, data about substance abuse and diversion are collected to the level of the specific formulation and manufacturer, including generic manufacturers, and rates are calculated quarterly.

2.1.1. Poison Center Program

The RADARS System Poison Center Program measures reports to poison centers involving people exposed to prescription opioid and stimulant medications. Fifty of the 57 poison centers operating in the US during the study period participated in the Poison Center Program, and 90.2 percent of the US population (excluding residents of Puerto Rico) resided in a covered area. Calls are initiated to poison centers by health care professionals or the general public, generally because of an acute medical event. Certified specialists in poison information collect data using narrative case notes and standardized data fields with definitions established by the American Association of Poison Control Centers (AAPCC, 2007). De-identified case-level data are transmitted to the RADARS System Poison Center Program, where research staff perform data integrity checks using standardized methods (Winter et al., 2012), and feedback is provided to improve data accuracy (Winter et al., 2013). The RADARS System Poison Center Program began collecting buprenorphine data in October, 2010.

For this analysis, only calls for which the reason for exposure was intentional abuse (“an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect, or some other psychotropic effect”) were included. A secondary analysis was performed on a subset of these patients for whom the route of exposure was “parenteral” (defined as, “an exposure resulting from the injection of a substance into the body”) or “inhalation/nasal.”

2.1.2. Drug Diversion Program

The RADARS System Drug Diversion Program measures illicit diversion by collecting reports of new police investigations, such as forged prescriptions, street drug “buys,” and pharmacy robberies, from law enforcement agencies. Approximately 260 police agencies in 49 states and the District of Columbia participate in the Drug Diversion Program. The RADARS System Drug Diversion Program began collecting buprenorphine data in October, 2010.

2.1.3. Treatment programs (Opioid Treatment Program and Survey of Key Informants' Patients Programs)

In the RADARS System Opioid Treatment Program (OTP) and Survey of Key Informants' Patients Program (SKIP), patients entering substance abuse treatment who choose to participate complete a 2-page survey about their substance abuse history. Abuse events are captured by asking subjects to report all opioid medications, “Used in [the] past month to get high.” Patients participating in the OTP and SKIP programs are predominately white (56%) male (52%) young adults (median age 31 years (interquartile range: 26–39 years)). During the study period, 83–86 percent of eligible patients chose to participate in the SKIP and 90–95 percent of eligible patients in the OTP. Approximately 79 federally certified treatment programs in 34 states participate in the OTP, and 125 treatment practices in 50 states participate in the SKIP. Data from the OTP and SKIP programs were combined for this analysis.

The primary analysis was performed on all abuse endorsements, and a secondary analysis was performed limiting data to cases in which the patient endorsed buprenorphine abuse by injection. The treatment programs began collecting buprenorphine data in April 2011.

2.1.4. College Survey Program

The RADARS System College Survey Program is an online questionnaire collecting data from self-identified students attending a 2- or 4-year college, university or technical school at least part-time during the specified sampling period. Data from approximately 2,000 participants are collected at the completion of the fall and spring academic semesters/quarters and at the end of the summer. Each sample is equally distributed across the four geographic regions of the United States (W, NW, S, and NE) and is composed of self-identified students who have agreed to be contacted to complete online surveys. Cases are defined as self-reported non-medical use of prescription opioid or stimulant medication by college students in the previous academic semester/quarter or over the summer break. Although non-medical use is not strictly synonymous with abuse (for example, using a roommate's oxycodone to treat pain from a sports injury is non-medical use but not abuse), in the vernacular of this report the terms are used interchangeably. Cases are assigned to the reported 3-digit ZIP code of the college student's residence. The College Survey Program began collecting buprenorphine data with the spring term 2011 survey.

2.2. Rate calculations

In order to account for differences in the availability of different drug formulations in the community, event ratios (rates) were calculated based on the number of persons filling prescriptions (“unique recipients of a dispensed drug,” URDD). One URDD is a single person filling a prescription for a specific product in a 3-digit zip code area covered by a RADARS System program in a year-quarter. Sales data used to calculate URDD were purchased from IMS Health Solutions (Parsippany, NJ). A complete description of URDD and the method by which URDD data are used to calculate rates have been published previously (Dasgupta et al., 2010; Smith et al., 2007). In order to provide context about changing prescribing of the three buprenorphine formulations over the study period, national-level URDD data were compared with population data from the US Census Bureau, using linear interpolation to produce quarterly data between available population data points.

Program event rates for each of the three formulations were calculated quarterly, and the averages of these rates, calculated using negative binomial regression, were used for the primary analysis. For each RADARS System program, the time period for analysis began during the first year/quarter for which buprenorphine data were collected and ended in the final quarter of 2012. Thus, the primary analysis contains 27 months of data in the Poison Center and Drug Diversion Programs, 21 months of data in the treatment programs, and 6 terms of data (approximately 18 months of sampling period

over a 2-year period) in the College Survey Program. Comparisons between the three formulations were made using negative binomial regression, and a two-tailed alpha level of 0.05 was used to define statistical significance. Data from the treatment programs were combined for the primary analysis, and OTP and SKIP data were reported separately in secondary analyses.

2.3. Geographic analysis

In an exploratory analysis, we examined state-level data about abuse and diversion of the three buprenorphine formulations. Maps were generated to show which formulation had the highest average abuse and diversion rates during the study period for each program, as defined above. Results were presented graphically; statistical comparisons were not performed on state-level data.

2.4. Human subjects protection

Overall operation of the RADARS System and of the Poison Center and College Survey Programs is approved by the Colorado Multiple Institution Institutional Review Board (IRB). In the Poison Center Program, the local IRB for each participating poison center also provides oversight for that center's participation. Operation of the Drug Diversion Program has been reviewed and classified as exempt by the Nova Southeastern University IRB. Operation of the OTP is approved by the National Development and Research Institutes IRB, and SKIP is approved by the Washington University IRB. Participants in the OTP, SKIP, and College Survey programs provided informed consent. Drug Diversion Program data are submitted by law enforcement personnel reporting about criminal investigations and do not involve any patient or arrestee data, and waiver of informed consent has been approved for all centers participating in the Poison Center Program. All study procedures were performed in accord with US FDA regulations and the Helsinki Declaration of 1975. No protected health information is transmitted between sites.

3. Results

3.1. Changes in prescribing over time

Between October 2010 and December 2012, the number of patients filling prescriptions for sublingual buprenorphine formulations increased faster than the US population as a whole, but the change was not similar over the three formulations (Fig. 1). The increase was greatest for combination film (228% increase relative to population). The number of patients filling prescriptions for single ingredient tablets increased 66% relative to population during the same period, while there was a 58% decrease in the number of patient filling prescriptions for combination tablets.

3.2. Poison center intentional-abuse cases involving buprenorphine

A total of 1,068 reports of intentional abuse of buprenorphine was received by the Poison Center Program over the 27-month study period. Adjusting for the number of patients filling prescriptions for each formulation (URDD), the average abuse rate for single ingredient tablets was 1.6 times that of combination film, and the average abuse rate for combination tablets was approximately 4 times that of the combination film (Table 1). These relationships were consistent over time (Fig. 2).

3.3. Drug diversion cases involving buprenorphine

A total of 1,374 cases of buprenorphine diversion was reported to the Drug Diversion Program over the 27-month study period. Adjusting for the number of patients filling prescriptions (URDD),

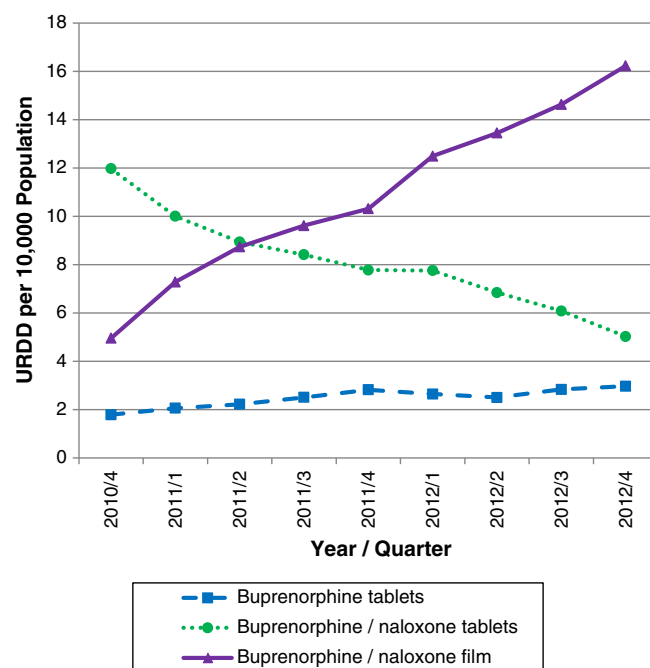


Fig. 1. Prescribing trends of buprenorphine sublingual formulations, United States, October 2010–December 2012. URDD: unique recipients of a dispensed drug. Data from IMS Global Health and US Census Bureau.

there were 6.4 times as many drug diversion cases involving single ingredient tablets and approximately 11 times as many cases involving combination ingredient tablets as cases involving the combination film (Table 1). These differences were statistically significant, and the relationships were consistent for all year-quarters studied (Fig. 2).

3.4. Reports of buprenorphine abuse by patients entering treatment

Overall, 4,669 patients (37.8% of all OTP and SKIP program participants) endorsed recent (past-month) buprenorphine abuse during the 21-month study period. Separate review of results from the OTP and SKIP showed no significant differences that would preclude combining data from the treatment programs for analysis (Supplemental Table A1 – on-line only).

In the treatment programs, availability-adjusted abuse rates for the single ingredient tablets exceeded those for the combination tablets or the combination film (Table 1). The abuse rate for the single ingredient tablets was 6.5 times that of combination film, while the combination tablet abuse rate was twice the combination film rate. The differences were statistically significant and consistent over time (Fig. 2).

3.5. Abuse among college students

A total of 183 students endorsed non-medical use of buprenorphine sublingual formulations. After adjusting for availability (URDD) in the students' home communities, average abuse rates for single ingredient tablets were 11 times the abuse rate for combination film, and the combination tablet abuse rate was 2.2 times the combination film rate (Table 1). These relationships are statistically significant and have been stable over the 6 terms of the study period (Fig. 2).

3.6. Abuse by non-oral routes

The Poison Center Program contained 229 reports of abuse by injection or snorting during the study period (21.4% of all abuse

Table 1

Average rates of abuse and diversion of three sublingual buprenorphine formulations, adjusted for drug availability, in the RADARS® System.

	Rate (program events per 10,000 URDD)	95% Confidence interval		Rate ratio compared with combination film	95% Confidence interval		Significance
Poison Center Program							
Buprenorphine tablets	1.5	1.2	1.9	1.6	1.1	2.4	$p = 0.009$
Buprenorphine/naloxone tablets	3.7	3.4	4.0	4.1	3.0	5.7	$p < 0.001$
Buprenorphine/naloxone film	0.9	0.8	1.1	Reference			
Drug Diversion Program							
Buprenorphine tablets	8.5	7.4	9.7	6.4	4.2	9.7	$p < 0.001$
Buprenorphine/naloxone tablets	13.1	12.3	14.0	10.9	7.3	16.4	$p < 0.001$
Buprenorphine/naloxone film	1.4	1.2	1.6	Reference			
Combined treatment programs (OTP + SKIP)							
Buprenorphine tablets	62.4	59.4	65.5	6.5	5.3	7.9	$p < 0.001$
Buprenorphine/naloxone tablets	20.8	19.8	21.9	2.2	1.8	2.7	$p < 0.001$
Buprenorphine/naloxone film	9.5	9.0	10.1	Reference			
College Survey Program							
Buprenorphine tablets	2.3	1.8	2.8	11.1	7.4	16.6	$p < 0.001$
Buprenorphine/naloxone tablets	0.4	0.3	0.6	2.2	1.4	3.4	$p < 0.001$
Buprenorphine/naloxone film	0.2	0.1	0.3	Reference			

URDD: unique recipients of a dispensed drug; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients Program.

Analytic period: Poison Center and Drug Diversion Programs, October 2010–December 2012; treatment programs, April 2011–December 2012; College Survey Program, spring term 2011–fall term 2012.

Poison Center Program data are limited to intentional abuse exposures. Abuse reports in the treatment programs refer to use “to get high” in the past month. Abuse reports in the College Survey Program refer to non-medical use in the past semester. Diversion reports in the Drug Diversion Program are law enforcement investigations initiated in the year/quarter.

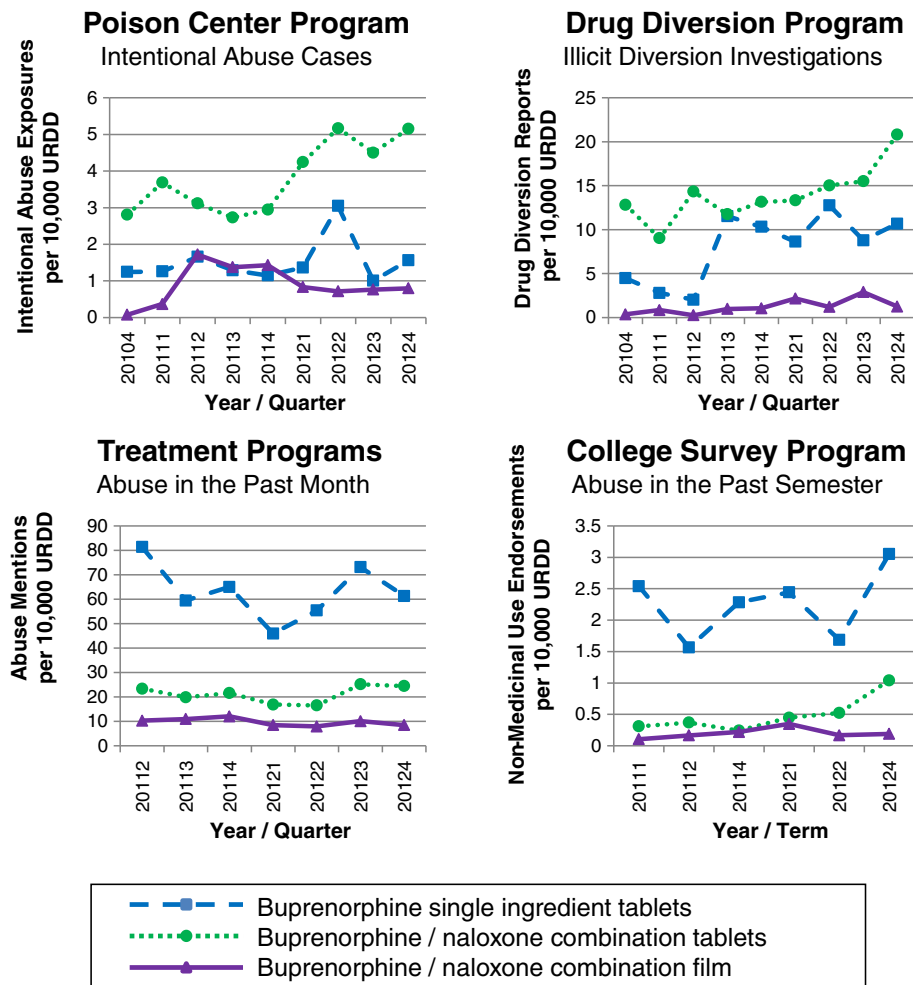


Fig. 2. Average rates of abuse and diversion of three sublingual buprenorphine formulations, adjusted for drug availability, in the RADARS® System. URDD: unique recipients of a dispensed drug.

Table 2

Average rates of abuse by non-oral routes of three buprenorphine sublingual formulations, adjusted for drug availability, in the RADARS® System Poison Center Program and combined treatment programs.

	Rate (abuse reports per 10,000 URDD)	95% Confidence interval		Rate ratio compared with combination film	95% Confidence interval		Significance
Poison Center Program: Parenteral + nasal routes only							
Buprenorphine tablets	0.6	0.4	0.8	3.5	2.1	5.8	$p < 0.001$
Buprenorphine/naloxone tablets	0.8	0.6	0.9	4.8	3.2	7.2	$p < 0.001$
Buprenorphine/naloxone film	0.2	0.1	0.2	Reference			
Combined treatment programs: Injection use only							
Buprenorphine tablets	27.0	25.1	29.1	20.0	15.4	25.6	$p < 0.001$
Buprenorphine/naloxone tablets	3.3	2.9	3.7	2.5	1.9	3.3	$p < 0.001$
Buprenorphine/naloxone film	1.3	1.2	1.6	Reference			

URDD: unique recipients of a dispensed drug.

Poison Center Program data are limited to intentional abuse exposures for which the reason for exposure is “parenteral” (injection) or “inhalation/nasal.” Treatment program data combine data from the RADARS System Opioid Treatment and Survey of Key Informants’ Patients Programs, with analysis limited to injection use exposures “to get high” in the past month.

Analytic period: Poison Center and Drug Diversion Programs, October 2010–December 2012; treatment programs, April 2011–December 2012; College Survey Program, spring term 2011–fall term 2012.

exposure reports) (Table 2). As with abuse overall, the largest abuse rates were seen with the combination tablets, and the lowest abuse rates were seen with the combination film.

A total of 1,186 patients reported injecting a buprenorphine sublingual formulation “to get high” in the 30 days prior to entering the treatment programs (Table 2). This number represents 25.4% of all buprenorphine sublingual formulation abuse endorsements. The availability-adjusted injection abuse rate for single ingredient buprenorphine tablets was 20 times the injection abuse rate for the combination film, and combination tablet injection was reported at a supply-adjusted rate 2.5 times that of combination film.

3.7. Geographic analysis

Fig. 3 shows the formulation with the greatest URDD rate of abuse and diversion in each state, using the same methods as the primary analysis for each program. Consistent with the nationwide data, in the Poison Center and Drug Diversion Programs, abuse and diversion rates of combination tablets exceeded that of other formulations in most states, while in the treatment and College Survey Programs, abuse of single ingredient tablets was most common in most states. Combination film rates exceeded those of other formulations in one state in the Poison Center Program (Mississippi), in two states in the College Survey Program (Indiana, Virginia), and in no states in the Drug Diversion Program or the treatment programs. No regional pattern was apparent.

4. Discussion

4.1. Comparison to previous published literature

The introduction of office-based treatment with buprenorphine has greatly expanded access to treatment for opioid dependence in the US, and the effectiveness of buprenorphine-based therapy has been well-established. These results show that all three sublingual buprenorphine formulations sold in the US are sometimes diverted for illegal sale and abused. However, abuse and diversion rates varied widely between formulations. The sublingual film combination product had lower abuse and diversion rates than either tablet formulation in all programs. The reasons for these relative priorities are not clear, but the relationships are statistically robust and have remained consistent over at least 2 years of observation in each program. Interestingly, the combination tablets consistently resulted in the greatest rates of calls to poison centers and drug diversion

investigations, while single ingredient tablets were responsible for greater abuse rates among patients entering substance abuse therapy and college students.

Buprenorphine tablet abuse and diversion has been described in the US and internationally, and is common in some settings (Strang, 1985; Yokell et al., 2011). One study reported that up to 20% of buprenorphine patients in France misused their prescription by intravenous administration (Auriacombe, Fatseas, Dubernet, Daulouede, & Tignol, 2004). From 2002–2008, the number of patients entering treatment for buprenorphine abuse at a large Finnish treatment center greatly exceeded the number of patients entering treatment for heroin abuse, with 83 percent of buprenorphine clients using their drug by injection (Uosukainen et al., 2013). Previous research from the US has shown that URDD rates of diversion and abuse of buprenorphine overall increased from 2003–2007 (Dasgupta et al., 2010).

Although direct comparison between drugs prescribed for analgesia and drugs prescribed to treat opioid dependence is problematic, some context is useful. In this study, availability-adjusted rates of buprenorphine abuse and diversion were often greater than recently reported abuse and diversion rates of opioid analgesics and methadone (Dart et al., 2012; Dasgupta et al., 2010; Severtson et al., 2013). During time period of the current study, RADARS System program event rates for buprenorphine sublingual formulations generally exceeded those of oxycodone immediate release products, probably because of the large population of patients who receive short-duration prescriptions for oxycodone and who are at very low risk for abuse. Conversely, hydromorphone abuse and diversion rates often exceeded buprenorphine rates. Unfortunately, a direct comparison the other opioid commonly used to treat opioid dependence, liquid methadone, is not possible because a large proportion of methadone is dispensed through federally-licensed opioid treatment programs and therefore not captured in our dispensing (URDD) data.

4.2. Limitations of this study

Measuring behavior that the person is actively trying to conceal is an imperfect process, and these results are subject to several additional limitations.

Drug Diversion Program data cannot determine the motivation of the ultimate customer of diverted buprenorphine. Illicit self-administration of buprenorphine to treat opioid dependence, reduce withdrawal symptoms, decrease the illicit use of other opioids, and decrease injection drug use have all been well-described (Hakansson, Medvedeo, Andersson, & Berglund, 2007; Monte, Mandell, Wilford,

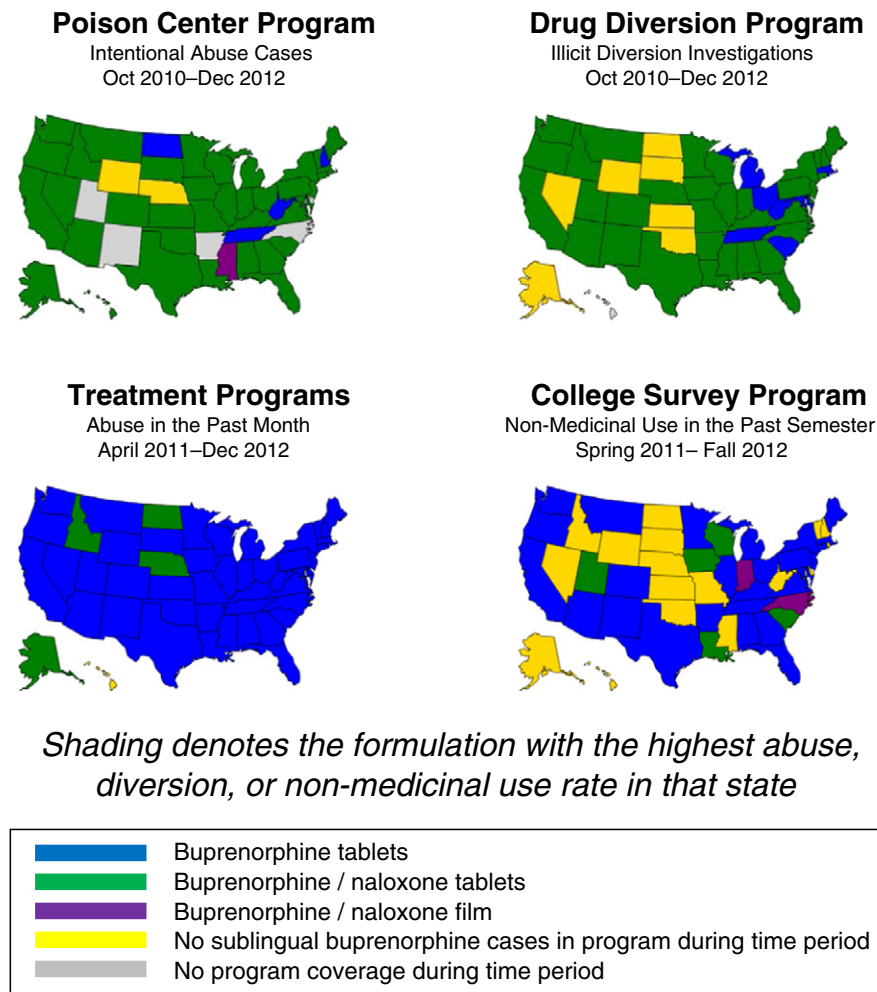


Fig. 3. Buprenorphine sublingual formulation with greatest average abuse and diversion rates in the RADARS® System, adjusted for drug availability, by state. Shading denotes the formulation with the highest rate.

Tennyson, & Boyer, 2009; Schuman-Olivier et al., 2010). The proportion of users of illicitly-obtained buprenorphine who seek euphoria, as opposed to self-medication, is tremendously variable internationally, and has not been established in the US (Yokell et al., 2011). Although the question administered in the OTP and SKIP surveys (“used in [the] past month to get high”) is explicit and designed to exclude self-medication, it is possible that some patients do not understand the instructions. The treatment program abuse rates do not distinguish between one-time and more frequent abuse of an opioid during the month prior to entering therapy, and the survey administered to all subjects collects only limited data about route of administration. Although structured qualitative interview research is being done in this population, to date these efforts have not focused on buprenorphine abuse (Cicero, Ellis, & Surratt, 2012). In addition, patients entering treatment may differ systematically from the larger population of prescription opioid abusers. Abuse and diversion rates may change as the film formulation becomes further established, a phenomenon that was observed for buprenorphine tablet formulations (Cicero, Surratt, & Inciardi, 2007).

4.3. Future research directions

There are several explanations for the observed differences that cannot be evaluated with these data and represent opportunities for future research.

4.3.1. Route of administration and other techniques associated with buprenorphine abuse

It is unclear whether buprenorphine tablet formulations can be manipulated for parenteral administration in a way that provides more euphoria (“a better high”) than the film formulation. If correct, this could be due to intrinsic advantages of the film formulation or due to longer access to and experience with the tablets. Quantitative data about routes of abuse and qualitative data garnered from interviews with buprenorphine abusers entering treatment may provide an explanation. Structured surveillance of common Internet forums devoted to illicit drug use shows that buprenorphine abusers prefer the tablets because they perceive the film formulation as “weak,” from a euphoria perspective. Focused investigations to understand specific features that make the film formulation less desired by abusers may lead to improved abuse-deterrent technology.

4.3.2. Diversion-deterrent packaging

Each combination film packet has a unique randomly numbered bar code; with future implementation of technology, this may eventually allow law enforcement agencies to identify the source of diverted medication. To our knowledge, the effectiveness of diversion-deterrent packaging has not been studied.

4.3.3. Dose and formulation

This study did not attempt to determine the rate of abuse and diversion of different strengths of each buprenorphine formulation.

Although a top-level analysis shows that the vast majority (84–90%) of patients filling prescriptions for each formulation obtained the 8 mg strength, it is possible that a detailed analysis of dose and formulation may yield additional insights.

4.3.4. Changing rates over time

Although this study was not designed to evaluate trends over time, abuse of the combination tablets and diversion of both single ingredient and combination tablets appeared to be increasing during the study period. Several subsequent major policy changes have occurred. The authorization of buprenorphine dispensing through opioid treatment programs (January 2013), introduction of generic combination tablets (February 2013), and introduction of mental health parity and formulary requirements in the Affordable Care Act (January 2014) will all lead to expanded access to buprenorphine therapy and may increase diversion and abuse. Close surveillance is needed to understand the societal impact of these changes.

4.4. Conclusion

Rates of abuse and diversion of buprenorphine tablets, with or without naloxone, consistently exceed those of buprenorphine/naloxone combination film.

Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jsat.2014.02.003>.

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References

- AAPCC (2007). *National Poison Data System (NPDS(R) Reference Manual. Part 2 – System information manual*. Washington, D.C.: American Association of Poison Control Centers.
- Amass, L., Ling, W., Freese, T. E., Reiber, C., Annon, J. J., Cohen, A. J., et al. (2004). Bringing buprenorphine-naloxone detoxification to community treatment providers: The NIDA Clinical Trials Network field experience. *American Journal on Addictions*, 13 (Suppl 1), S42–S66.
- Auriacombe, M., Fatseas, M., Dubernet, J., Daulouede, J. P., & Tignol, J. (2004). French field experience with buprenorphine. *American Journal on Addictions*, 13 (Suppl 1), S17–S28.
- Cicero, T. J., Ellis, M. S., & Surratt, H. L. (2012). Effect of abuse-deterrent formulation of OxyContin. *New England Journal of Medicine*, 367, 187–189.
- Cicero, T. J., Surratt, H. L., & Inciardi, J. (2007). Use and misuse of buprenorphine in the management of opioid addiction. *Journal of Opioid Management*, 3, 302–308.
- Comer, S. D., & Collins, E. D. (2002). Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. *Journal of Pharmacology and Experimental Therapeutics*, 303, 695–703.
- Daniulaityte, R., Falck, R., & Carlson, R. G. (2012). Illicit use of buprenorphine in a community sample of young adult non-medical users of pharmaceutical opioids. *Drug and Alcohol Dependence*, 122, 201–207.
- Dart, R. C., Cicero, T. J., Surratt, H. L., Rosenblum, A., Bartelson, B. B., & Adams, E. H. (2012). Assessment of the abuse of tapentadol immediate release: The first 24 months. *Journal of Opioid Management*, 8, 395–402.
- Dasgupta, N., Bailey, E. J., Cicero, T., Inciardi, J., Parrino, M., Rosenblum, A., et al. (2010). Post-marketing surveillance of methadone and buprenorphine in the United States. *Pain Medicine*, 11, 1078–1091.
- FDA (2002). Subutex and suboxone approved to treat opioid dependence. Retrieved December 11, 2012 from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191521.htm>.
- Fiellin, D. A., & O'Connor, P. G. (2002). Clinical practice. Office-based treatment of opioid-dependent patients. *New England Journal of Medicine*, 347, 817–823.
- Fudala, P. J., & Johnson, R. E. (2006). Development of opioid formulations with limited diversion and abuse potential. *Drug and Alcohol Dependence*, 83 (Suppl 1), S40–S47.
- Hakansson, A., Medvedeo, A., Andersson, M., & Berglund, M. (2007). Buprenorphine misuse among heroin and amphetamine users in Malmo, Sweden: Purpose of misuse and route of administration. *European Addiction Research*, 13, 207–215.
- Inciardi, J. A., Surratt, H. L., Cicero, T. J., Kurtz, S. P., Martin, S. S., & Parrino, M. W. (2009). The “black box” of prescription drug diversion. *Journal of Addictive Diseases*, 28, 332–347.
- Johanson, C. E., Arfken, C. L., di Menza, S., & Schuster, C. R. (2012). Diversion and abuse of buprenorphine: Findings from national surveys of treatment patients and physicians. *Drug and Alcohol Dependence*, 120, 190–195.
- Johnson, R. E., Jaffe, J. H., & Fudala, P. J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. *JAMA*, 267, 2750–2755.
- Maremmiani, I., Pani, P. P., Pacini, M., & Perugi, G. (2007). Substance use and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. *Journal of Substance Abuse Treatment*, 33, 91–98.
- Mattick, R. P., Kimber, J., Breen, C., & Davoli, M. (2008). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews*, CD002207.
- Mendelson, J., & Jones, R. T. (2003). Clinical and pharmacological evaluation of buprenorphine and naloxone combinations: Why the 4:1 ratio for treatment? *Drug and Alcohol Dependence*, 70 (2 Suppl), S29–S37.
- Monte, A. A., Mandell, T., Wilford, B. B., Tennyson, J., & Boyer, E. W. (2009). Diversion of buprenorphine/naloxone coformulated tablets in a region with high prescribing prevalence. *Journal of Addictive Diseases*, 28, 226–231.
- Schuman-Olivier, Z., Albanese, M., Nelson, S. E., Roland, L., Puopolo, F., Klinker, L., et al. (2010). Self-treatment: Illicit buprenorphine use by opioid-dependent treatment seekers. *Journal of Substance Abuse Treatment*, 39, 41–50.
- Schwarz, R., Zelenev, A., Bruce, R. D., & Altice, F. L. (2012). Retention on buprenorphine treatment reduces emergency department utilization, but not hospitalization, among treatment-seeking patients with opioid dependence. *Journal of Substance Abuse Treatment*, 43, 451–457.
- Severtson, S. G., Bartelson, B. B., Davis, J. M., Munoz, A., Schneider, M. F., Chilcoat, H., et al. (2013). Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. [Research Support, Non-U. S. Gov't]. *The journal of pain : official journal of the American Pain Society*, 14, 1122–1130.
- Smith, M. Y., Schneider, M. F., Wentz, A., Hughes, A., Haddox, J. D., & Dart, R. (2007). Quantifying morbidity associated with the abuse and misuse of opioid analgesics: A comparison of two approaches. *Clinical Toxicology (Philadelphia, Pa.)*, 45, 23–30.
- Strang, J. (1985). Abuse of buprenorphine. *Lancet*, 2, 725.
- Sullivan, L. E., Moore, B. A., Chawarski, M. C., Pantalon, M. V., Barry, D., O'Connor, P. G., et al. (2008). Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. *Journal of Substance Abuse Treatment*, 35, 87–92.
- Uosukainen, H., Kauhanen, J., Voutilainen, S., Fohr, J., Paasolainen, M., Tiitonen, J., et al. (2013). Twelve-year trend in treatment seeking for buprenorphine abuse in Finland. *Drug and Alcohol Dependence*, 127, 207–214.
- Walsh, S. L., & Eissenberg, T. (2003). The clinical pharmacology of buprenorphine: Extrapolating from the laboratory to the clinic. *Drug and Alcohol Dependence*, 70 (2 Suppl), S13–S27.

- Walsh, S. L., Preston, K. L., Stitzer, M. L., Cone, E. J., & Bigelow, G. E. (1994). Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clinical Pharmacology and Therapeutics*, 55, 569–580.
- Winter, E. J., Davis, J., Bucher-Bartelson, B., Westberry, R., Green, J. L., & Lavonas, E. J. (2012). Systematic misclassification in product-specific coding of poison center data: The example of buprenorphine in the RADARS® System Poison Center program. *Clinical Toxicology (Philadelphia, Pa.)*, 50.
- Winter, E. J., Martinez, E. M., Lavonas, E. J., Bucher Bartelson, B., Poppish, L., Green, J. L., et al. (2013, September). Micromedex® Clarification of Suboxone® Products Increases Coding Accuracy in the RADARS® System Poison Center Program. Paper presented at the North American Congress of Clinical Toxicology (NACCT) Annual Meeting, Atlanta, GA.
- Yokell, M. A., Zaller, N. D., Green, T. C., & Rich, J. D. (2011). Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: An international review. *Current Drug Abuse Reviews*, 4, 28–41.